#12

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Art Unit	:	122
Examiner	:	W. Teoli
Applicant(s)	:	Mahendra I. Amin and Jay A. Campbell
Serial Number	:	Continuation of 06/898,676
Filed	:	
For	:	CRYSTALLINE CEPHALOSPORIN HYDROHALIDE SALTS

Commissioner of Patents and Trademarks
Washington, DC 20231

DECLARATION UNDER 37 CFR 1.132

Sir:

I, Mahendra I. Amin, being duly warned that willful false statements and the like are punishable by fine or imprisonment or both (18 USC 1001) and may jeopardize the validity of the above-captioned application or any patent issuing thereon, state and declare that:

All statements herein made on my own knowledge are true and all statements herein made on information and belief are believed to be true.

1. I am one of the named co-inventors in the above-identified application.

2. I am a Senior Research Scientist-Pharmacy. I received a PhD degree in Physical Pharmacy from the University of Wisconsin in 1967. I have worked for The Upjohn Company (hereinafter Upjohn) since 1967. My responsibilities at Upjohn include research to find appropriate pharmaceutical formulations for the cephalosporin antibiotic compounds ceftiofur sodium and ceftiofur hydrochloride.

3. Analysis of the data by computer (copies of computer printout sheets attached) shows that crystalline ceftiofur hydrochloride in the solid, powder state is estimated to have an estimated useful shelf life of greater than 60.00 months at 25°C. In comparison, the analysis data for amorphous ceftiofur sodium powder indicates an estimated shelf life of only about 0.46 month at

25°C. These data suggest that ceftiofur hydrochloride has about 120 times longer shelf life advantage over ceftiofur sodium as a solid form cephalosporin antibiotic. This advantage suggests that the ceftiofur hydrochloride can be considered for a larger variety of pharmaceutical dosage forms than can the ceftiofur sodium salt.

4. Crystalline ceftiofur hydrochloride in a two percent W/V glyceryl monostearate peanut oil gel pharmaceutical suspension formulation (100 mg/ml activity for ceftiofur hydrochloride), the ceftiofur hydrochloride was estimated to have a shelf life of about 21.3 weeks at 25°C. versus an estimated shelf life of only 2.81 weeks at 25°C. for the ceftiofur sodium in the same two percent glyceryl monstearate vehicle formulation and 100 mg/ml activity for ceftiofur sodium. Additionally, it has been found that for crystalline ceftiofur hydrochloride in a two percent W/V glyceryl monostearate peanut oil gel pharmaceutical suspension formulation (20 mg/ml activity for ceftiofur hydrochloride), the ceftiofur hydrochloride was estimated to have a shelf life of a minimum of 18 months at 25°C.

5. The shelf life of the crystalline ceftiofur hydrochloride in an oil formulation can be further increased by addition of pharmaceutical adjuvant so that the ceftiofur hydrochloride formulation can be marketed. In contrast, the shelf life of ceftiofur sodium in an oil formulation is expected to be extremely low and addition of additives thereto is not expected to increase the shelf life of ceftiofur sodium enough to increase the shelf life of the formulation such that it could be marketed.

6. The better shelf stability of ceftiofur hydrochloride, relative to ceftiofur sodium, permits this hydrochloride salt to be formulated into suspension formulations for oral or parenteral delivery routes of administration over a longer time after manufacture, packaging and storage.

7. The longer stability of the crystalline solid form of ceftiofur hydrochloride, relative to ceftiofur sodium, allows this solid hydrochloride salt to be packaged separately, e.g., in a two-compartment vial, one compartment containing the solid hydrochloride salt drug powder, and the other containing the diluting liquid pharmaceutical vehicle for mixing extemporaneously as needed in the field by the veterinary or medical doctor to treat a variety of bacterial infections in pigs, cats, dogs and chickens as well as

cattle, whereas ceftiofur sodium due to its shorter stability would not be preferred for this type of packaging and use.

8. Further, since crystalline ceftiofur hydrochloride has better stability than the ceftiofur sodium in the solid powder state, the hydrochloride salt is better amenable to formulating it into pharmaceutical formulations for oral dosage forms, e.g., such as in tablet and capsule form.

Date: February 16, 89

Mahendra I. Amin

Mahendra I. Amin

Attachments:

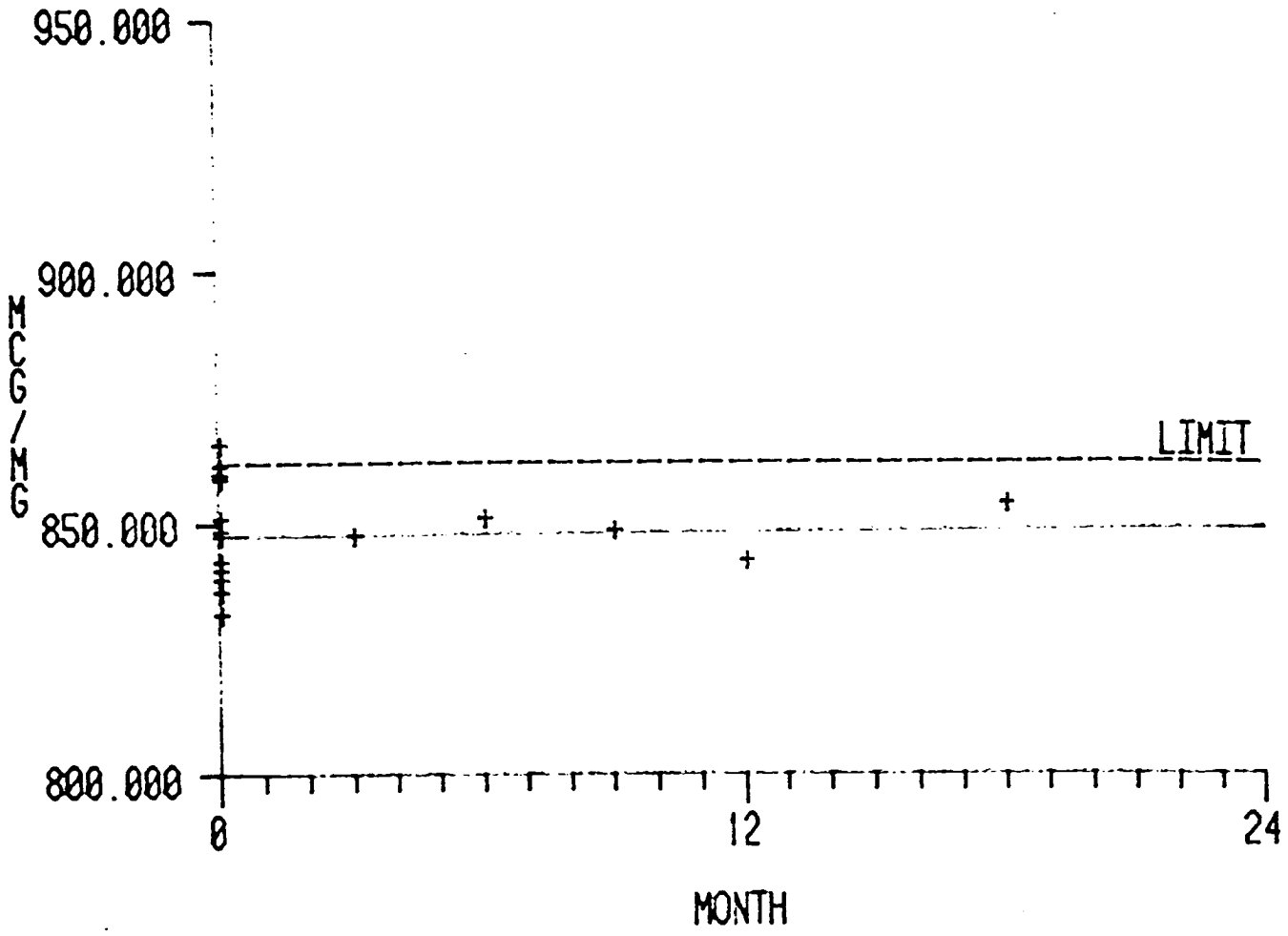
- Computer analysis of shelf stabilities
- Stability in pharmaceutical vehicles

DATAT - DATA TABLE FOR VET. 27-Oct-87 01:49 PM
EDP #: V200017
TITLE: CEFTIOFUR HCL BULK DRUG MICRONIZED PROCESS A-1
TEMPERATURE: 25 DEG C
REL. HUMIDITY: AMBIENT
ASSAY FOR: CEFTIOFUR FREE ACID
RESULTS ARE EXPRESSED AS: MCG/MG

MONTH	18985MIA31
0.00	847.0
0.00	831.0
0.00	838.0
0.00	859.0
0.00	861.0
0.00	858.0
0.00	865.0
0.00	842.0
0.00	840.0
0.00	848.0
0.00	850.0
0.00	836.0
3.00	847
6.00	850
9.00	848
12.00	842
18.00	853

REGRESSION ANALYSIS SUMMARY

TITLE: CEFTIOFUR HCL BULK DRUG MICRONIZED PROCESS A-1
ASSAY FOR: CEFTIOFUR FREE ACID
ASSAY METHOD: HPLC



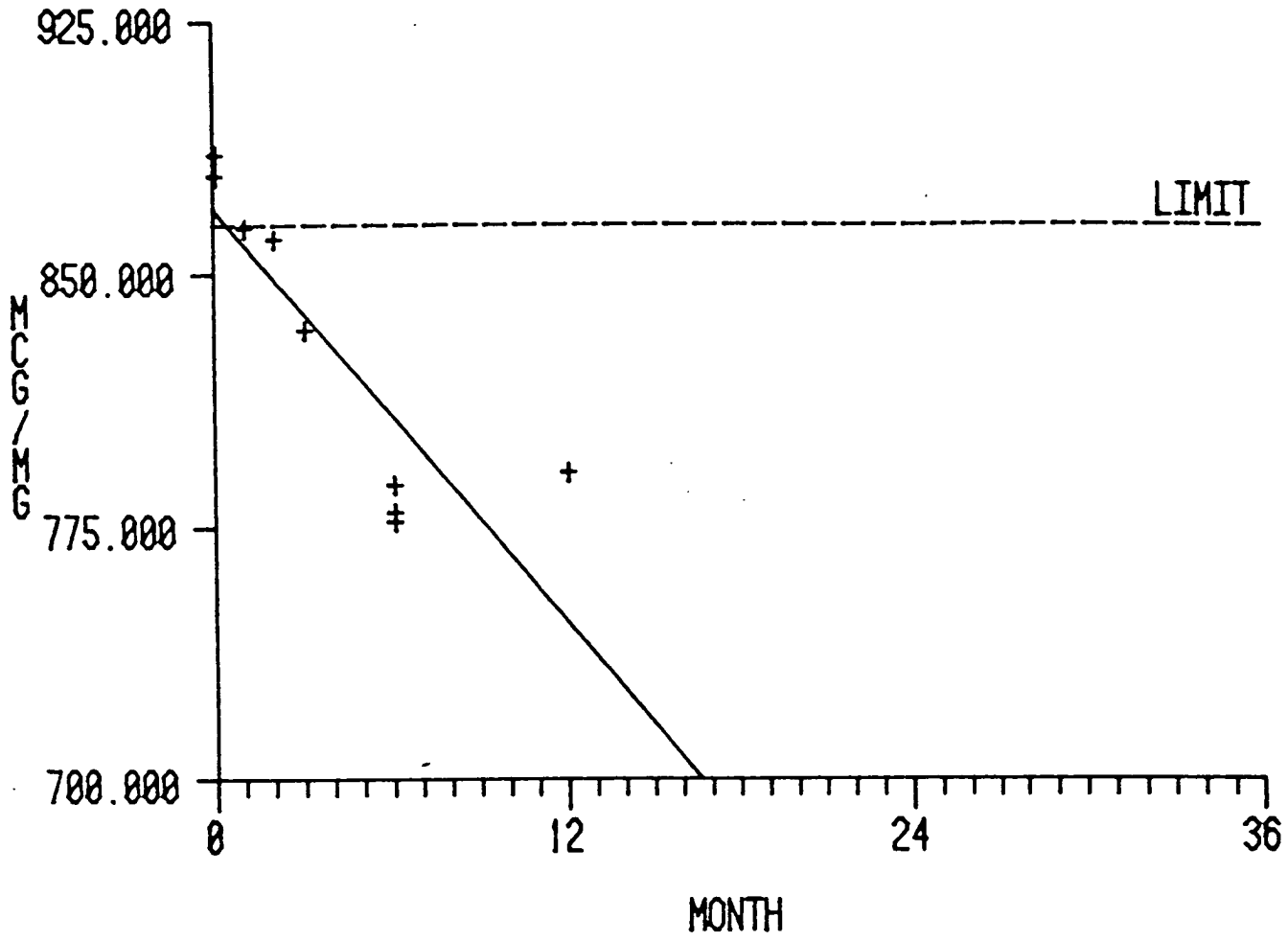
THE ESTIMATED (NONSIGNIFICANT) RATE OF CHANGE IS 0.0651
MCG/MG PER MONTH
LOWER LIMIT IS 862.0000 MCG/MG
ESTIMATED SHELF LIFE IS GREATER THAN 60.00 MONTH
LOTS TESTED: 18985MIA31
STORAGE CONDITIONS: 25 DEG C AMBIENT
SOURCE LOT 18851KDM46

DATAT - DATA TABLE FOR VET. 27-Oct-87 01:49 PM
EDP #: V200006
TITLE: CEPHALOSPORIN SODIUM BULK DRUG U64279E
TEMPERATURE: 25 DEG C
REL. HUMIDITY: AMBIENT
ASSAY FOR: CEFTIOFUR FREE ACID
RESULTS ARE EXPRESSED AS: MCG/MG

MONTH	17689-RKV-129 NO FURTHER TESTING SCHEDULED FOR THIS STUDY
0.00	878
0.00	884
0.00	884
1.00	863
2.00	859.0
3.00	832
6.00	786
6.00	775
6.00	778
8.51	N.R.
12.00	790

REGRESSION ANALYSIS SUMMARY

TITLE: CEPHALOSPORIN SODIUM BULK DRUG U64279E
ASSAY FOR: CEFTIOFUR FREE ACID
ASSAY METHOD: HPLC



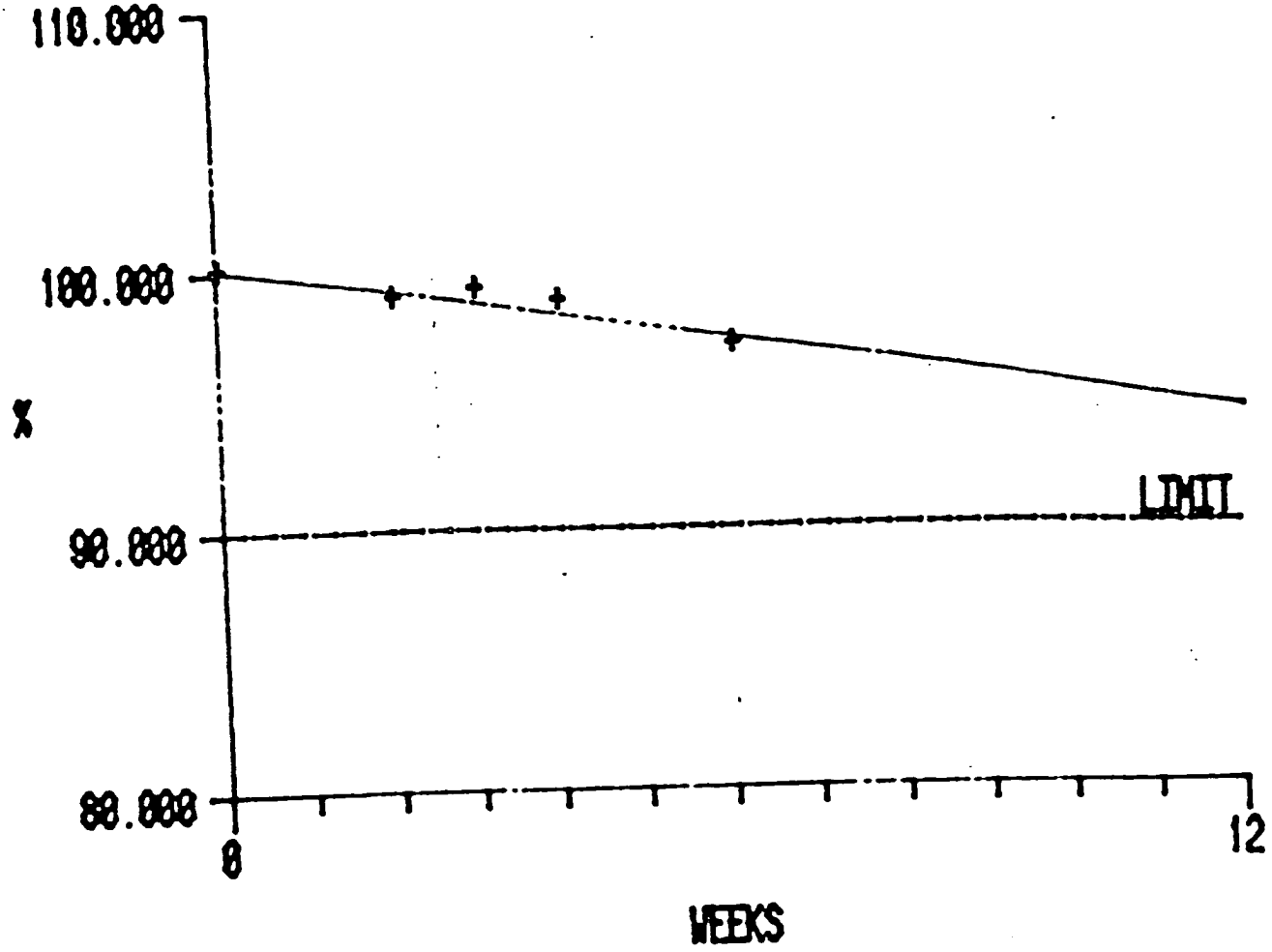
THE ESTIMATED (SIGNIFICANT) RATE OF CHANGE IS -10.2155
MCG/MG PER MONTH
LOWER LIMIT IS 865.0000 MCG/MG
ESTIMATED SHELF LIFE IS 0.46 MONTH
LOTS TESTED: 17689-RKV-129
STORAGE CONDITIONS: 25 DEG C AMBIENT

FORMULATIONS

Stability of ceftiofur HCl vs. ceftiofur sodium in two percent glyceryl monostearate as a vehicle.

GRESSION ANALYSIS SUMMARY

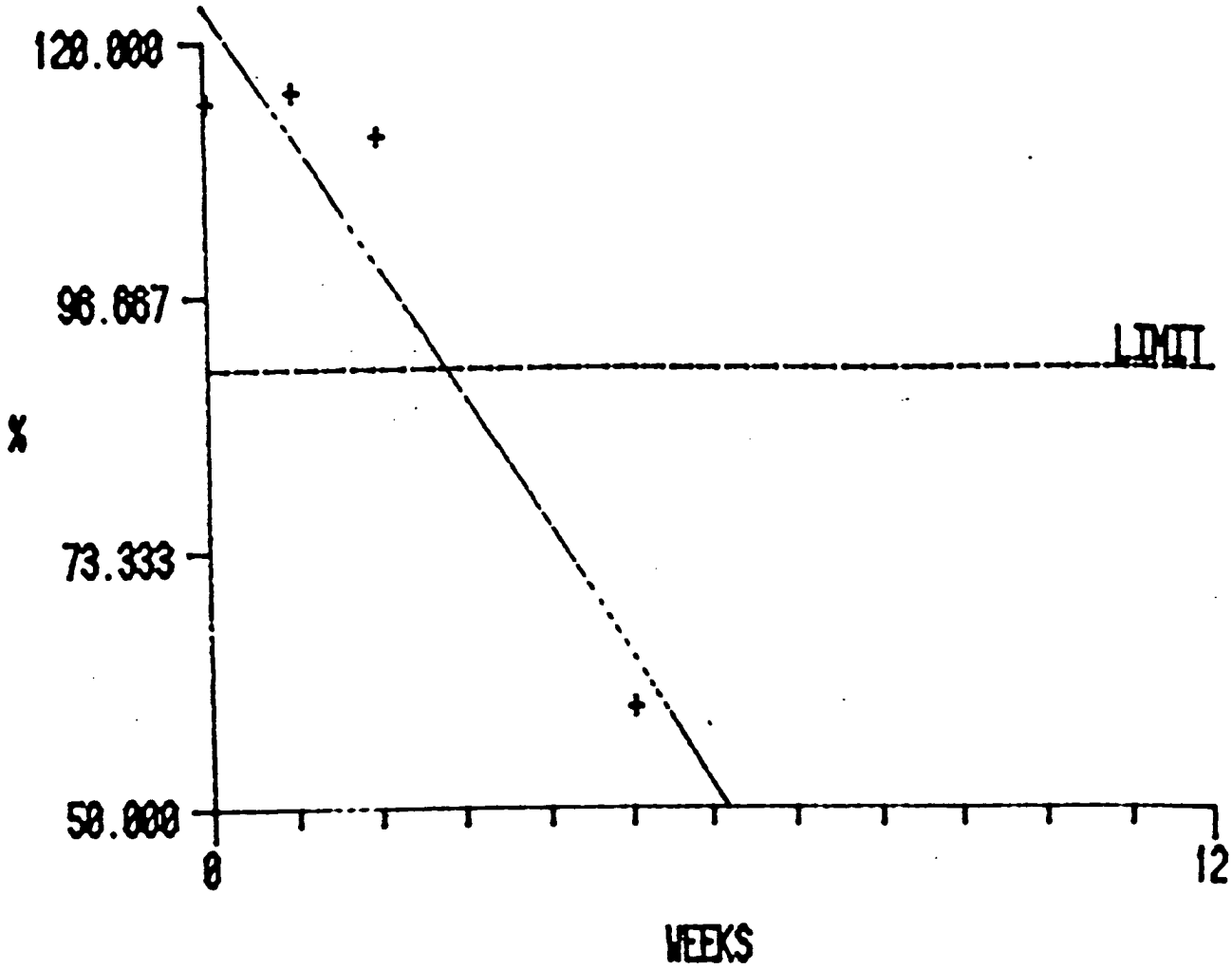
TITLE: CEFTIOFUR HYDROCHLORIDE OIL SUSPENSIONS
ASSAY FOR: ASSAY BY HPLC
ASSAY METHOD: CEPHALOSPORIN HCL (HPLC)



THE ESTIMATED (SIGNIFICANT) RATE OF CHANGE IS -0.4750
% PER WEEKS
LOWER LIMIT IS 90.0000 %
ESTIMATED SHELF LIFE IS 21.27 WEEKS
MINIMUM ESTIMATED SHELF LIFE IS 13.89 WEEKS
LOTS TESTED: 17944-NSH-000E
STORAGE CONDITIONS: RT
2% GLYCERYL MONOSTEARATE PEANUT OIL GEL

REGRESSION ANALYSIS SUMMARY

TITLE: SODIUM CEFTIOFUR OIL SUSPENSIONS
ASSAY FOR: ASSAY BY HPLC
ASSAY METHOD: CEPHALOSPORIN SODIUM (HPLC)



THE ESTIMATED (NONSIGNIFICANT) RATE OF CHANGE IS -11.8500
% PER WEEKS
LOWER LIMIT IS 90.0000 %
ESTIMATED SHELF LIFE IS 2.81 WEEKS
LOTS TESTED: 16387-SRP-114-GL
STORAGE CONDITIONS: 25 DEG C AMBIENT
2% GLYPOG